CLAIMS

WHAT IS CLAIMED IS:

1. A method of synthesizing a poly(oxazolone) homopolymer via a nitroxide-mediated controlled living free radical polymerization reaction, the method comprising:

providing a reactive polymer propagating species having a free radical moiety;

reacting the reactive polymer propagating species with a first vinyl-functionalized oxazolone monomer, thereby producing an extended reactive polymer propagating species;

coupling a nitroxide capping compound with the extended reactive polymer propagating species, thereby forming an intermediary dormant species;

dissociating the nitroxide capping compound from the intermediary dormant species, thereby regenerating the extended reactive polymer propagating species; and

repeating the reacting, coupling, and dissociating steps with additional vinyl-functionalized oxazolone monomers, thereby synthesizing the poly(oxazolone) homopolymer via a nitroxide-mediated controlled living free radical polymerization reaction.

2. The method of claim 1, wherein the oxazolone monomer comprises 2-vinyl-4,4-dimethyl-5-oxazolone (VDMO), 2-(4'-vinyl)-phenyl-4,4-dimethyl-5-oxazolone (VPDMO), 2-isopropenyl-4,4-dimethyl-5-oxazolone (IPMO), 2-vinyl-3-Oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-vinyl-4,4-diethyl-5(4H)-oxazolone, 2-vinyl-3-oxa-1-azaspiro[4.4]non-1-en-4-one, 2-vinyl-4,4-dibutyl-5(4H)-oxazolone, 2-vinyl-4-ethyl-4-methyl-5(4H)-oxazolone, 4-methyl-4-propyl-2-vinyl-2-oxazolin-5-one, or 2-vinyl-4-methyl-4-phenyl-5(4H)-oxazolone.

3. The method of claim 1, wherein the nitroxide capping compound comprises a nitrosyl compound having an α-secondary carbon.

4. The method of claim 3, wherein the nitroxide capping compound comprises 1,1-dimethylethyl 2-methyl-1-phenylpropyl nitroxide or, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO).

5. The method of claim 1, wherein repeating the reacting, coupling, and dissociating steps generates a polymer having a polydispersity of less than or equal to 1.20 as determined by size exclusion chromatography.

6. The method of claim 5, wherein repeating the reacting, coupling, and dissociating steps generates a polymer having a polydispersity of less than or equal to 1.15.

7. The method of claim 5, wherein repeating the reacting, coupling, and dissociating steps generates a polymer having a polydispersity of less than or equal to 1.10.

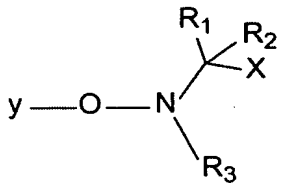
8. The method of claim 1, wherein providing the reactive polymer propagating species comprises:

a) providing a first monomer comprising the vinyl-functionalized oxazolone compound;

b) providing an alkoxyamine compound capable of dissociating into a first nitroxide portion and a second free radical portion; and

c) reacting the second free radical portion of the dissociated alkoxyamine compound with the first monomer, thereby forming a oxazolone propagating species.

9. The method of claim 8, wherein the alkoxyamine comprises a compound having the formula



wherein X comprises a chemical moiety that destabilizes the Y-O bond, Y comprises the second free radical portion, and R1, R2 and R3 independently comprise a hydrocarbon or substituted hydrocarbon moiety.

10. The method of claim 8, wherein the alkoxyamine comprises N-(1,1-dimethylethyl)-α-(1-methylethyl)-N-(1-phenylethoxy)-benzenemethanamine or 2,2,6,6-tetramethyl-1-(1-phenylethoxy)-piperidine.

11. The method of claim 8, wherein the nitroxide capping compound used in the coupling step comprises the first nitroxide portion of the alkoxyamine compound.

12. The method of claim 8, wherein providing the alkoxyamine compound further comprises providing a 5% molar excess of free nitroxide.

13. The method of claim 1, wherein the reacting, coupling, and dissociating steps are performed at 100-130 °C for between 1 and 24 hours.

14. The method of claim 13, wherein the reacting, coupling, and dissociating steps are performed at 120-125 °C for between 4 and 16 hours.

15. The method of claim 13, wherein the reacting, coupling, and dissociating steps are performed at 123°C for 4 hours.

16. The method of claim 1, wherein the additional vinyl-functionalized oxazolone monomers comprises the first vinyl-functionalized oxazolone monomer.

17. The method of claim 1, wherein the additional vinyl-functionalized oxazolone monomers comprises a mixture of two or more oxazolone monomers.

18. The method of claim 1, further comprising:

reacting the poly(oxazolone) homopolymer with an amine-functionalized agent to produce an agent-poly(oxazolone) conjugate.

19. The method of claim 18, wherein the amine-functionalized agent comprises a therapeutic agent, a contrast agent, a diagnostic agent, or a targeting agent.

20. The method of claim 1, further comprising:

reacting the poly(oxazolone) homopolymer with a hydroxyl-containing agent in the presence of a base to produce an ester-functionalized agent-poly(oxazolone) conjugate.

21. The method of claim 20, wherein the hydroxyl-containing agent comprises a therapeutic agent, a contrast agent, a diagnostic agent, or a targeting agent.

22. A poly(oxazolone) homopolymer prepared by the method of claim 1, wherein the homopolymer has a polydispersity of less than or equal to 1.20 as determined by size exclusion chromatography.

23. A poly(oxazolone) homopolymer prepared by the method of claim 1, wherein the homopolymer has a polydispersity of less than or equal to 1.15 as determined by size exclusion chromatography.

24. A poly(oxazolone) homopolymer prepared by the method of claim 1, wherein the homopolymer has a polydispersity of less than or equal to 1.10 as determined by size exclusion chromatography.

25. A method of synthesizing an oxazolone-containing copolymer via a nitroxide-mediated controlled living free radical polymerization reaction, the method comprising:

providing a plurality of monomers comprising a first set of vinyl-functionalized oxazolone compounds and a second set of second monomers;

providing a reactive polymer propagating species having a free radical moiety;

reacting the reactive polymer propagating species with a member of the plurality of monomers, thereby producing an extended reactive polymer propagating species;

coupling a nitroxide capping compound with the extended reactive polymer propagating species and forming an intermediary dormant polymer species;

dissociating the nitroxide capping compound from the intermediary dormant polymer species, thereby regenerating the extended reactive polymer propagating species; and

repeating the reacting, coupling, and dissociating steps with additional member monomers, thereby synthesizing the oxazolone-containing copolymer via a nitroxide-mediated controlled living free radical polymerization reaction.

26. The method of claim 25, wherein the first set of vinyl-functionalized oxazolone compounds comprises VDMO, VPDMO, IDMO, 2-vinyl-3-oxa-1-azaspiro[4.5]dec-1-en-4-one, 2-vinyl-4,4-diethyl-5(4H)-oxazolone, 2-vinyl-3-oxa-1-azaspiro[4.4]non-1-en-4-one, 2-vinyl-4,4-dibutyl-5(4H)-oxazolone, 2-vinyl-4-ethyl-4-methyl-5(4H)-oxazolone, 4-methyl-4-propyl-2-vinyl-2-oxazolin-5-one, or 2-vinyl-4-methyl-4-phenyl-5(4H)-oxazolone or a combination thereof.

27. The method of claim 25, wherein the first set of vinyl-functionalized oxazolone monomers comprises a mixture of two or more oxazolone monomers.

28. The method of claim 25, wherein the second set of second monomers comprises styrene, substituted styrene, alkyl acrylate, substituted alkyl acrylate, alkyl methacrylate, substituted alkyl methacrylate, acrylic acid, methacrylic acid, acrylonitrile, methacrylonitrile, acrylamide, N-alkylacrylamide, N-alkylmethacrylamide, N,N-dialkylacrylamide, N,N-dialkylmethacrylamide, isoprene, butadiene, ethylene, vinyl acetate, vinylidene chloride, vinylidene fluoride, vinyl chloride, vinyl fluoride, tetrafluoroethylene, 4-vinyl pyridine, 3-vinyl pyridine, 2-vinyl pyridine, N-vinyl amides or a combination thereof.

29. The method of claim 25, wherein the second set of second monomers comprises styrene monomers.

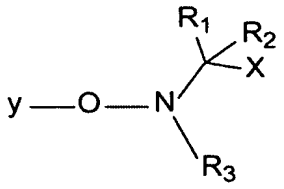
30. The method of claim 25, wherein the nitroxide capping compound comprises a nitrosyl compound having an α-secondary carbon.

31. The method of claim 30, wherein the nitroxide capping compound comprises 1,1-dimethylethyl 2-methyl-1-phenylpropyl nitroxide or, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO).

32. The method of claim 25, wherein providing the reactive polymer propagating species comprises reacting a first member of the plurality of monomers with an initiator compound capable of generating a free radical.

33. The method of claim 32, wherein the initiator compound comprises an alkoxyamine compound capable of dissociating into a first nitroxide portion and a second free radical portion.

34. The method of claim 32, wherein the alkoxyamine comprises a compound having the formula



wherein X comprises a chemical moiety that destabilizes the Y-O bond, Y comprises the second free radical portion, and R1, R2 and R3 independently comprise a hydrocarbon or substituted hydrocarbon moiety.

35. The method of claim 32, wherein the alkoxyamine comprises N-(1,1-dimethylethyl)-α-(1-methylethyl)-N-(1-phenylethoxy)-benzenemethanamine or 2,2,6,6-tetramethyl-1-(1-phenylethoxy)-piperidine.

36. The method of claim 32, wherein the nitroxide capping compound comprises the first nitroxide portion of the alkoxyamine compound.

37. The method of claim 25, wherein providing the plurality of monomers comprises providing the first set of vinyl-functionalized oxazolone compounds and repeating the

reacting, coupling, and dissociating steps prior to providing the second set of second monomers, thereby synthesizing an oxazolone-containing block copolymer.

38. The method of claim 25, wherein providing the plurality of monomers comprises providing a mixture of the first set of vinyl-functionalized oxazolone compounds and the second set of second monomers, thereby synthesizing an oxazolone-containing random copolymer.

39. The method of claim 38, wherein the plurality of monomers comprises 50% vinyl-functionalized oxazolone compounds and 50% second monomers.

40. The method of claim 38, wherein the plurality of monomers comprises 10% vinyl-functionalized oxazolone compounds and 90% second monomers.

41. The method of claim 38, wherein the plurality of monomers comprises 90% vinyl-functionalized oxazolone compounds and 10% second monomers.

42. The method of claim 25, further comprising:

reacting the poly(oxazolone) copolymer with an amine-functionalized agent to produce an agent-poly(oxazolone) copolymer conjugate.

43. The method of claim 18, wherein the amine-functionalized agent comprises a therapeutic agent, a contrast agent, a diagnostic agent, or a targeting agent.

44. The method of claim 1, further comprising:

reacting the poly(oxazolone) copolymer with a hydroxyl-containing agent in the presence of a base to produce an ester-functionalized agent-poly(oxazolone) copolymer conjugate.

45. The method of claim 20, wherein the hydroxyl-containing agent comprises a therapeutic agent, a contrast agent, a diagnostic agent, or a targeting agent.

46. A poly(oxazolone) copolymer prepared by the method of claim 25, wherein the copolymer has a polydispersity of less than or equal to 1.20 as determined by size exclusion chromatography.

47. A poly(oxazolone) homopolymer prepared by the method of claim 25, wherein the copolymer has a polydispersity of less than or equal to 1.15 as determined by size exclusion chromatography.

48. A poly(oxazolone) homopolymer prepared by the method of claim 25, wherein the copolymer has a polydispersity of less than or equal to 1.10 as determined by size exclusion chromatography.

49. A poly(oxazolone) copolymer prepared by the method of claim 25, wherein the copolymer has a weight average molecular weight greater than about 5000 Da and a polydispersity of less than or equal to 1.20 as determined by.

50. A poly(oxazolone) copolymer prepared by the method of claim 25, wherein the copolymer has a weight average molecular weight between 10,000 Da and 100,000 Da.

51. A poly(oxazolone) copolymer prepared by the method of claim 25, wherein the copolymer has a weight average molecular weight between 25,000 Da and 35,000 Da.

52. A method of synthesizing an active agent-conjugated poly(oxazolone) polymer via a nitroxide-mediated controlled living free radical polymerization reaction, the method comprising:

providing a plurality of monomers comprising a first set of vinyl-functionalized oxazolone compounds and an optional second set of second monomers;

providing a reactive polymer propagating species having a free radical moiety;

reacting the reactive polymer propagating species with a member of the plurality of monomers, thereby producing an extended reactive polymer propagating species;

coupling a nitroxide capping compound with the extended reactive polymer propagating species and forming an intermediary dormant polymer species;

dissociating the nitroxide capping compound from the intermediary dormant polymer species, thereby regenerating the extended reactive polymer propagating species; and

repeating the reacting, coupling, and dissociating steps with additional member monomers;

providing a functionalized active agent; and

conjugating the functionalized active agent to the oxazolone-containing polymer, thereby synthesizing the active agent-conjugated oxazolone-containing polymer via a nitroxide-mediated controlled living free radical polymerization reaction.

53. The method of claim 52, wherein the first set of vinyl-functionalized oxazolone compounds comprises VDMO, VPDMO, IDMO, 2-vinyl-3-oxa-1-azaspiro[4.5]dec-1-en-4-

one, 2-vinyl-4,4-diethyl-5(4H)-oxazolone, 2-vinyl-3-oxa-1-azaspiro[4.4]non-1-en-4-one, 2-vinyl-4,4-dibutyl-5(4H)-oxazolone, 2-vinyl-4-ethyl-4-methyl-5(4H)-oxazolone, 4-methyl-4-propyl-2-vinyl-2-oxazolin-5-one, or 2-vinyl-4-methyl-4-phenyl-5(4H)-oxazolone or a combination thereof.

54. The method of claim 52, wherein the optional second set of second monomers comprises styrene, substituted styrene, alkyl acrylate, substituted alkyl acrylate, alkyl methacrylate, substituted alkyl methacrylate, acrylic acid, methacrylic acid, acrylonitrile, methacrylonitrile, acrylamide, N-alkylacrylamide, N-alkylmethacrylamide, N,N-dialkylacrylamide, N,N-dialkylmethacrylamide, isoprene, butadiene, ethylene, vinyl acetate, vinylidene chloride, vinylidene fluoride, vinyl chloride, vinyl fluoride, tetrafluoroethylene, 4-vinyl pyridine, 3-vinyl pyridine, 2-vinyl pyridine, N-vinyl amides or a combination thereof.

55. The method of claim 52, wherein the nitroxide capping compound comprises 1,1-dimethylethyl 2-methyl-1-phenylpropyl nitroxide or, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO).

56. The method of claim 52, wherein the functionalized active agent comprises one or more therapeutic agents, contrast agents, diagnostic agents, or targeting agents.

57. The method of claim 56, wherein the therapeutic agent comprises one or more peptides, proteins, antiproliferative agents, anti-cancer compounds, chemotherapeutic agents, antibiotics, antiviral agents, antiparasitic compounds, nucleic acids, or a combination thereof.

58. The method of claim 56, wherein the contrast agent comprises an MRI contrast agent, an X-ray contrast agent, a PET contrast agent, a CT contrast agent, an ultrasonography contrast agent, a fluorescent probe, a chromophore, a nucleic acid, a radioisotope, or a combination thereof.

59. The method of claim 52, wherein the functionalized active agent comprises an amine-functionalized or a hydroxyl-functionalized active agent.

60. The method of claim 52, wherein the functionalized active agent is coupled to the polymer via an enzymatically-cleavable linker.

61. The method of claim 52, wherein the poly(oxazolone) polymer comprises an oxazolone homopolymer.

62. The method of claim 52, wherein the poly(oxazolone) polymer comprises a random copolymer or a block copolymer.

63. The method of claim 52, wherein the functionalized agent for conjugation with the polymer comprises an amine-functionalized contrast agent or alcohol- functionalized contrast agent.

64. A pharmaceutical formulation comprising an active agent-conjugated poly(oxazolone) polymer prepared by the method of claim 52.

65. The pharmaceutical formulation of claim 64, wherein a molar ratio of therapeutic agent to polymer is between about 100:1 to about 1:1.

66. The pharmaceutical formulation of claim 64, wherein a molar ratio of therapeutic agent to polymer is about 20:1.

67. A contrast agent comprising an active agent-conjugated poly(oxazolone) polymer prepared by the method of claim 52.

68. The contrast agent conjugate of claim 67, wherein a molar ratio of contrast agent to polymer is between about 100:1 and about 1:1.

69. The contrast agent conjugate of claim 67, wherein a molar ratio of contrast agent to polymer is about 20:1